Faculty of Medicine – University of Lisbon

Academic year 2015/2016

FACULDADE DE MEDICINA LISBOA

Risk factors for recurrence of chronic subdural hematoma: a series of 257 surgically treated patients

Master thesis

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Resumo

Introdução: Apesar das diferentes abordagens terapêuticas atualmente existentes para o tratamento do hematoma subdural crónico (HSDC), a recidiva pós-cirúrgica mantém-se uma complicação frequente. O objetivo deste estudo é identificar fatores de risco para recidiva de HSDC.

Métodos: Realizámos um estudo caso-controlo retrospetivo com uma série de casos consecutivos de HSDC tratados cirurgicamente. Relacionámos as seguintes variáveis com o risco de recidiva de HSDC: género, idade, localização do HSDC, terapêutica com antiagregantes ou anticoagulantes, trombocitopénia e utilização de dreno pós-operatório.

Resultados: Dos 257 doentes analisados, 40 (15.6%) apresentaram recidiva do HSDC. Verificou-se maior taxa de recidiva nos doentes mais jovens (p <0.05) e tendência a recidiva nos doentes medicados com anticoagulantes e naqueles em que não foi utilizado dreno subdural pós-operatório (p <0.2). As outras variáveis não se associaram a maior risco de recidiva. Os doentes com recidiva apresentaram maior morbilidade (p <0.05).

Conclusões: Na série analisada, a recidiva de HSDC esteve associada a maior morbilidade pós-cirúrgica, e a idade mais jovem constituiu um fator de risco para recidiva. A medicação habitual com anticoagulantes e a ausência de dreno subdural pós-operatório poderão constituir outros fatores de risco.

Palavras-chave: Hematoma subdural crónico; recidiva; idade; anticoagulantes; dreno

Abstract

Introduction: In spite of the current different therapeutic approaches for the treatment of chronic subdural hematoma (CSDH), post-operative recurrence remains a frequent complication. The aim of this study is to identify risk factors for recurrence of CSDH.

Methods: We conducted a retrospective case-control study with a series of consecutive surgically treated cases of CSDH. The following variables were analyzed as potential risk factors for recurrence of CSDH: gender, age, location of CSDH, treatment with antiaggregants or anticoagulants, thrombocytopenia and use of postoperative drain.

Results: From a total of 257 patients analyzed, 40 (15.6%) presented with recurrent CSDH. We observed a higher recurrence rate in younger patients (p <0.05) and a tendency towards recurrence in patients treated with anticoagulants and in those who did not receive a subdural post-operative drain (p <0.2). The other variables were not associated with higher risk of recurrence. Patients with recurrence presented higher morbidity (p <0.05).

Conclusions: In this series, recurrence of CSDH was associated with increased post-operative morbidity, and younger age was a risk factor for recurrence. Usual medication with anticoagulants and the absence of subdural post-operative drain may represent other risk factors.

Key-words: Chronic subdural hematoma; recurrence; age; anticoagulants; drain

List of abbreviations:

- ACE: angiotensin converting enzyme
- aPTT: activated partial thromboplastin time
- BHC: burr-hole craniostomy
- CHLO: Centro Hospitalar Lisboa Ocidental
- CSDH: chronic subdural hematoma
- CT: computerized tomography
- DBC: dural border cell
- GCS: Glasgow coma scale
- INR: international normalized ratio
- MRI: magnetic resonance imaging
- PlGF: placental growth factor
- SD: standard-deviation
- SDH: subdural hematoma
- TDC: twist-drill craniostomy
- VEGF: vascular endothelial growth factor

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I. Introduction

1. Definition

A subdural hematoma (SDH) is a collection of blood between the inner layer of the dura mater and the arachnoid mater. It is one of the most common type of traumatic intracranial mass lesion [1]. The cause of this neurosurgical entity is frequently the tearing of the bridging veins, which connect the cortical surface of the brain to a dural sinus [1], after a head trauma [2].

SDHs may be classified as acute, subacute or chronic, based on the amount of time elapsed since the beginning of the bleeding, which is important to determine the best treatment to each type [3]. It is generally considered that SDHs are acute until the first 72 hours after the injury, subacute between 3-7 days, and chronic when they are ≥ 3 weeks [1, 3]. While an acute SDH occurs usually in younger adults after a major trauma, a chronic subdural hematoma (CSDH) affects mainly the elderly after a less important injury and it takes a few weeks or months until it becomes clinically apparent.

2. Epidemiology

CSDH is one of the most frequent diagnoses in neurosurgery. The incidence of CSDH is estimated at 1.7-18 per 100.000 people, increasing to 58 per 100.000 people in patients above 65 years old [1, 4-6]. It has a peak incidence between the sixth and the seventh decades of life, and the average age of patients is approximately 63 years old [1, 2]. As the number of old people increases in population, the incidence of CSDH is expected to double by the year 2030 [1, 4]. CSDH affects predominantly men with a male-to-female ratio of 3:1 [1, 7]. Recurrence of CSDH after the treatment is one of the most frequent complications with a median incidence of 15% reported in the literature, ranging from 0 to 30% [1]. CSDHs are bilateral in 20-25% of the cases [1]. Bilateral SDHs are more common in infants, because the adhesions existing in the subdural space are absent at birth and develop with aging [1].

3. Pathophysiology, etiology and risk factors

A CSDH is a delineated blood collection in the space between the dura mater and the arachnoid, enclosed within a hematoma capsule [8]. The subdural space is a virtual space that does not exist in physiological conditions, because the dura and the arachnoid are bound by a layer of dural border cells (DBC), made especially of fibroblasts [1, 4, 9]. This layer is relatively loose, as it has no tight junctions or intercellular collagen, and it is crossed by the bridging veins. The tearing of these veins causes a leakage of blood into the DBC layer and creates an acute SDH [1, 8, 9]. The incapacity of resorption of small acute SDHs will result in a CSDH [1, 2]. The shearing of the DBC layer generates an inflammatory reaction by the fibroblasts, which appears to be the initial stimulus of the pathophysiology of CSDH [9]. In 20-30% of the cases, the cause of the SDH is an arterial rupture [4].

The tearing of the bridging veins seems to be, therefore, the main cause of CSDH. This tearing can have a non-traumatic origin, such as cerebrovascular lesions (p.e. arteriovenous malformations), infections, brain tumors (p.e. convexity meningiomas) [8], or a traumatic one, which is definitely more frequent. Traumatic causes include direct head injuries, but also indirect trauma, in which the point where the traumatic force is applied is not in the cranium, but, due to sudden acceleration and deceleration forces, the brain is affected. Head trauma may occur in several situations, such as falls, previous neurosurgery or during labor [10]. The majority of CSDHs are caused by trivial mild indirect head trauma [1, 2, 11]. Elderly and male gender are considered risk factors of CSDH, as these groups have a higher tendency to head injury [1, 12].

In addition to these causes, many factors increase the vulnerability of the bridging veins and the risk of developing a CSDH, such as cerebral atrophy (a common and physiological condition in the elderly), deformation of the cranial vault during its development, and low intracranial pressure [8, 12]. When there is brain atrophy, the arachnoid is dragged away from the dura mater, which remains attached to the skull, stretching the bridging veins passing through the subdural space [1].

Hematogenic factors play also an important role in CSDH's pathophysiology, as they may increase the patient's tendency to bleed. Coagulopathies, which includes medical conditions having a bleeding tendency, such as liver cirrhosis (p.e. by chronic alcoholism), chronic renal failure, hematologic disorders, chemotherapy, but also

therapy with anticoagulants or antiplatelet agents are well-known risk factors of CSDH [10, 11].

After the tearing of the bridging veins, the blood leakage and the inflammatory reaction by the fibroblasts of the DBC layer, the blood collection undergoes a series of changes, with leucocyte infiltration, neoangiogenesis, microhemorrhage, local coagulopathy, collagen synthesis, fibrin deposition and excessive local fibrinolysis and anticoagulation with liquefaction of the hematoma [1, 9]. The development of CSDH is a dynamic process [9].

After approximately two weeks, an inner (cortical) and outer (dural) neomembrane is formed within the DBC layer [1]. The thicker outer membrane corresponds to the meningeal layer of the dura mater, and it develops into several stages until it becomes extremely inflamed and vascularized by giant capillaries, which present an incomplete basement membrane and allow an easy and repeated bleeding [8, 9].

The factors responsible for the maintenance and growth of CSDH are still unclear and have been studied for decades, leading to different theories. One of the most currently accepted theories is the microbleeds theory, in which the growth of the hematoma is explained by recurrent microhemorrhages from the giant and fragile capillaries of the neomembrane [1]. The anticoagulant and profibrinolytic theory postulates that there is an excess of fibrinolytic and anticoagulant factors in the neomembrane itself, which causes liquefaction of the subdural blood clots and continuous hemorrhage from the sinusoidal vessels [1, 8, 9]. An infiltration of eosinophils in the outer membrane, observed in several studies, may also contribute to the local hyperfibrinolysis and recurrent bleedings, as their granules contain plasminogen [9]. The inflammatory and growth factors theory suggests that the inflammation around the CSDH is accompanied by a high concentration of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) [1, 9]. These angiogenic factors allow continuous formation of neovessels, which are hyperpermeable, causing the expansion of the hematoma [1, 9]. Probably the multiple factors described in these three theories cause the maintenance and enlargement of CSDH [1].

4. Clinical presentation

Most commonly, the presentation is subacute or chronic, after a minor head injury. The CSDH develops slowly, under low pressure, and it takes a variable period until it becomes clinically apparent. The severity of symptoms vary from mild (confusion, gait disturbance, dementia, language problems, incontinence) to severe (hemiplegia, aphasia, seizures, coma), and general symptoms are often present (headache, fatigue, nausea and vomiting, vertigo) [1, 13, 14].

In a study with 500 patients with CSDH, the most common symptoms were gait disturbance (63%), hemiparesis (58.6%) and headache (38.2%) [10]. Dementia, incontinence, consciousness disturbance, vomiting, seizures, anisocoria and motor aphasia were also registered [10]. Headache was more frequent in younger patients, and dementia occurred more often in bilateral CSDHs [10]. In another study, with patients over 90 years old, the leading symptoms were hemiparesis and gait disturbance, followed by disturbance of consciousness and speech disturbance [15].

Usually, the younger the patient is, more severe and acute the symptoms are, because of the age-related cerebral atrophy that allows the hematoma to reach a larger size without triggering any neurologic signs [1, 16]. Because CSDH affects mainly the elderly, the severe symptoms are less common than the mild ones. Patients with CSDH can be asymptomatic, making the diagnosis difficult.

5. Diagnosis

For the diagnosis of CSDH it is fundamental to have a high index of suspicion [2]. It should be considered in any patient presenting one or more symptoms above described, with or without a history of trauma. After collecting clinical history and performing physical examination, brain imaging should be performed. The mainstay for diagnosis of CSDH is computerized tomography (CT) [1, 2, 7, 8]. A typical CT scan image of a CSDH is a crescent-shaped iso- to hypodens collection between the inner table of the skull and the surface of the affected cerebral hemisphere [1, 17].

As CSDH is a dynamic lesion, its appearance on CT scans varies with its time. During the acute phase of the hematoma (< 3 days), the blood collection is hyperdens, becoming isodens in its subacute phase (3 days to 3 weeks) and hypodens in the chronic

phase (≥ 3 weeks) [1, 2]. It is not rare to find a heterogeneously dens image of the hematoma, because of the repeated microhemorrhages [2]. Subacute hematomas may be harder to identify, as they are isodens. The location of the CSDH is usually in the fronto-parietal region over the convexity, but may also occur in the cranial base [17].

Besides the hematoma itself, other CT features can be found due to his mass effect: sulcal effacement, midline shift and obliteration of the basal cisterns [2]. These signs can be absent when there is a bilateral CSDH.

Magnetic resonance imaging (MRI) is more accurate than CT and, therefore, it may be required in patients with isodens subacute, bilateral, or small hematomas [2]. MRI allows for precise evaluation of the hematoma thickness, its margins, and the identification of its membranes and internal structures, even in small CSDHs [1]. Nevertheless, CT is preferred over MRI, because of its accessibility, shorter study time, and lower cost [1, 2, 8]. Other exams, such as contrast-enhanced CT, cerebral angiography, and scintigraphy are usually not required.

6. Management

The treatment of CSDH has been studied over the years and it is still subject of hundreds of current studies. Both conservative and surgical therapies have been proposed, but recurrence rates and complications remain an issue and are not fully understood. Today, it is widely accepted that the choice of treatment will depend on the clinical presentation and the radiographic appearance of the hematoma [1, 4]. Therefore, an asymptomatic patient with a minor CSDH is best managed conservatively or remaining under monitoring, whereas a symptomatic patient with a large hematoma would rather benefit from surgical evacuation. The treatment of patients with CSDH with mass effect, but without neurologic symptoms, is controversial, and there is no sufficient data to support the decision [1]. The hematoma's size may play an important role in the decision to perform surgery, but evidence-based absolute cutoffs sizes still do not exist [1]. Generally accepted cutoffs for the indication of surgery are maximum hematoma thickness exceeding that of the skull, or greater than 1 cm [1].

Some of the conservative therapies of CSDH that have been suggested are the use of corticosteroids, angiotensin converting enzyme (ACE) inhibitors, osmotic diuretics such

as mannitol, and tranexamic acid [1]. Spontaneous resolution of CSDHs has also been reported [18, 19]. Further research is clearly necessary, before one can truthfully rely on these therapies. On the other hand, surgical drainage is considered an effective treatment, and it can be achieved with twist-drill craniostomy (TDC), burr-hole craniostomy (BHC), or craniotomy [20]. These are the most common surgical procedures, and for each one numerous variations have been developed. The lack of high quality and well performed studies makes it difficult to identify the most effective surgical technique for CSDH [1].

With TDC, a small opening of 5-10 mm in the scalp is produced and a twist drill hole is placed in the direction of the longitudinal axis of the hematoma [1, 3]. A catheter is inserted into the subdural space, and it is removed when at least 20% of the hematoma is drained and/or when there is clinical improvement, which occurs in mean of 2.1 days [3]. A low pressure shunt valve can be introduced to prevent air reflux [3]. The decompression of the brain occurs more slowly than in other surgical procedures, avoiding the presumed rapid pressure shifts that may be associated with complications, such as intracerebral hemorrhage [3]. TDC is less invasive and can be performed under local anesthesia at the bedside. Therefore, it is an attractive option for patients with several comorbidities who are poor surgical candidates [4]. However, this technique is most effective in cases of completely liquefied blood collections with no membranes, and it can be associated with an increased risk of infection when performed at the bedside [4]. There are varying results between studies that compared outcomes of TDC vs. BHC or craniotomy. One study, in 1997, concluded that TDC had lower mortality and reoperation rates than BHC [21]. More recent studies revealed that TDC had a similar or even superior mortality rate and a significantly higher recurrence rate, when compared to BHC [4, 20].

BHC allows a larger opening (5-30 mm) in the scalp and it is usually performed under general anesthesia [4, 20, 22]. BHC seems to be, in the present time, the most common treatment for CSDH [4, 19, 20]. It has the best cure to complication ratio, and it appears to be more effective in treating recurrent hematomas than TDC [23]. There are many variations of this technique, regarding the number of burr-holes (one or two are the most common options), the need of intraoperative irrigation, the use of closed-system drainage after the surgery or not, the localization of the drain (subgaleal or subdural), and the post-operative procedures [4]. Despite the large number of studies

comparing the results achieved with these different variations of BHC, the most efficient method remains unclear. It seems that two burr-holes are as effective as one burr-hole in the CSDH management [17, 24]. Evidence favors the use of irrigation fluid to wash out the hematoma, even though it can increase the risk of pneumocephalus and infection [7]. Regarding drainage use, it is becoming more evident that inserting closed-system drainage after surgery improves the patient's outcome, by decreasing recurrence and mortality rates [20]. When comparing subdural and subgaleal drains, no significant difference in recurrence and functional outcome was found, at least at 3 months after surgery, but there was a tendency of lower rate of recurrence after subdural drain and a tendency of lower mortality after subgaleal drain [25]. Post-operative procedures such as maintaining a lying flat position and adequate intravenous hydration have been thought to reduce recurrence rates, but the complications of immobility (infections, deep venous thrombosis, etc.) also need to be considered [4, 26].

Craniotomy requires general anesthesia, and involves the turning of a larger (> 30 mm) free bone flap, irrigation and evacuation of the CSDH, following the replacement of the flap [7]. This was the treatment of choice until the mid-1960s, because it offered the surgeon a maximal exposure of the brain and the ability to excise membranes in the subdural space, allowing the brain re-expansion [7, 20]. This is the most invasive option for the treatment of CSDH, requires a greater operative time, entails a greater blood volume loss [4] and is associated with higher rates of morbidity [6, 14, 23]. Despite these, craniotomy is still the best option for evacuation of recurrent organized, calcified and with several thick membranes CSDHs, and for primary evacuation of a CSDH presenting a substantial acute component [4, 7, 14].

Many other surgical techniques have been proposed, such as oxygen instillation, middle meningeal artery embolization, ommaya reservoir implantation with repeated punctures and subduroperitoneal shunting [4]. Further studies are needed in order to recommend the generalized adoption of these procedures.

7. Post-operative complications, recurrence rates and outcome

Possible post-operative complications include: failure of the brain to re-expand and/or reaccumulation of the subdural fluid, leading to recurrence of CSDH (0-30%) [1]; seizures (1-23%) [1, 3]; intracerebral hemorrhage (0,7-5%) [1, 3]; infections (surgical site infection, subdural empyema, etc.) (2%) [1, 3] and tension pneumocephalus (0-10%) [1, 3]. Non-surgical complications related to the hospitalization (hospital-acquired infections, venous thromboembolism) and to the patient's previous diseases can always occur. All surgery-related complications are more common in elderly, polymorbid and debilitated patients [3].

The most important complication of CSDH is recurrence needing a repeated drainage [7]. Recurrence rates vary widely in literature, but the most contemporary consensus is that the reoperation rate is about 10-20% [7]. The risk factors for recurrence, discussed in several studies, are variable and include: age, alcoholism, diabetes, cerebral atrophy, use of anticoagulation or antiplatelet medication, poor clinical state at presentation, poor Glasgow coma scale (GCS) and Glasgow outcome scale, bilateral CSDH, highly dens hematoma on CT, thick hematoma on CT or MRI, intraoperative visualization of defective brain re-expansion and thick membranes, post-operative midline shift, pneumocephalus and presence of septum or multiple membranes in the subdural space [1, 7, 27, 28]. Intraoperative insertion of a closed system drainage after surgical procedure is the only proven factor that reduces recurrence rates [1].

Mortality in patients with CSDH varies from 0–32%, and morbidity from 0–25% [7]. Important prognostic factors include age, GCS score or clinical state at presentation, presence of medical comorbidities and coagulopathy [7]. In a series of 500 patients treated with BHC with closed-system drainage, 89.4% had a good recovery, 8.4% showed no change, 2.2% worsened and 1.2% died [10].

8. Objective

The aim of this study is to identify risk factors for recurrence in a series of surgically treated CSDHs.

II. Materials and methods

1. Study design

We conducted a retrospective case-control study using data from all patients consecutively operated for chronic or subacute SDH at Centro Hospitalar Lisboa Ocidental (CHLO), which includes Hospital Egas Moniz and Hospital São Francisco Xavier, in Lisbon, Portugal, between January 2011 and December 2014. The study was made by a 6th year medicine student as his master's degree final project, under orientation of a 5th year Neurosurgery Resident at CHLO. Patients' data was analyzed by the authors, using the institutional computing database and the surgical reports book, between February and October 2015. Patients were informed, during their hospitalization, that their clinical data could be used for medical research.

Patients admitted in the two aforementioned hospitals presenting symptoms consistent with chronic or subacute SDH underwent a CT scan and if the diagnosis was confirmed they were hospitalized. We defined CSDH as a hypodens blood collection in the subdural space, and subacute SDH when the blood collection was isodens. In this study, both conditions were included and they were simply designated CSDH. Surgery was performed whenever a patient with a CSDH scan was symptomatic. Presenting symptoms included headaches, gait disturbances, confusion, hemiparesis, aphasia, disorientation and seizures. A BHC, under general anesthesia, was performed as the standard surgical technique. Exclusion criteria were patients presenting concomitantly chronic and acute SDHs. If missing data was not possible to complete by clinical record consultation, patients were excluded from statistical analysis.

We collected the following data for each patient at admission: gender, age, clinical presentation (GCS and presence of focal neurologic deficits), usual medication (antiplatelet or anticoagulant drugs, ACE inhibitors) and laboratory tests (platelet count, international normalized ratio [INR], activated partial thromboplastin time [aPTT]). We also gathered information about the surgical procedure and outcomes after surgery (recurrence, morbidity and mortality). Recurrence was defined as need of a second surgical procedure, in the first two months after surgery, due to persistence or re-accumulation of CSDH in the same location, proven by CT scan. The criteria for re-operation were worsening or recurrence of neurological deficits [29]. For patients who had recurrent CSDH (undergoing, therefore, at least two surgeries), we only analyzed

their first procedure. Mortality included death in the first month after surgery. Morbidity was defined as any clinical complication occurring after surgery, other than recurrence or death. Data regarding follow-up after discharge was collected from out-patient clinics records. Follow-up appointments were usually held at 1, 3 and 6 months after surgery.

2. Hospitalization and operative method

Essentially the same surgical technique was employed for CSDH by the several neurosurgeons of CHLO. Hematoma evacuation was done via one or two burr-holes, and irrigation was made with isotonic saline, under sedation or general anesthesia. Two-burr-hole technique was the most used. Closed system drainage (subgaleal or subdural) was left in place when the risk of recurrence was predicted as higher. If a patient taking antiaggregants or anticoagulants was clinically stable, the surgery was postponed until the washout of the medication, but during that period patients were admitted and closely monitored. If an urgent surgery was necessary, the adequate correction, either with platelets or coagulation factors, was done.

After surgery, patients received adequate intravenous hydration and were maintained in a lying flat position, to help the brain re-expansion. If a drain was left in place, it was removed 48-72h after surgery, usually after a new CT evaluation.

Instead of BHC, craniotomy was performed mostly to treat recurrent cases.

3. CT surveillance

All patients underwent a CT scan to confirm the diagnosis prior to the operation. Routine postoperative CT was performed before drain removal (or 72h after surgery, if no drain was placed), and repeated before each medical appointment, until no further control was needed.

4. Statistical analysis

The variables analyzed as being potential risk factors for CSDH recurrence were age, gender, presence of bilateral CSDH, medication with antiplatelet agents or anticoagulants before surgery, presence of thrombocytopenia before surgery, absence of

post-operative drain, either subdural or subgaleal. For each variable *p* value with 95% confidence interval was determined using Fisher's exact test (two-tailed). For age, analysed as a continuous variable, the τ test was used. These calculations were obtained using GraphPad® online software. A trend was defined when $p < 0.2$ [30].

III. Results

The trial profile is shown in Figure 1. A total of 261 patients were operated for CSDH during this period. Four patients were excluded from the study: 2 due to missing data and 2 because they presented with both chronic/subacute and acute SDH. Of the 257 patients analyzed, 40 had recurrence – recurrence rate of 15.6%. Most patients (251) underwent BHC, whereas 6 were treated with craniotomy.

The characteristics of the patients are noted in Table 1. Approximately 63% of our patients were male and mean age was 76 years old (ranging from 37 to 98, median 78). Mean age among men was slightly lower than among women (75 vs. 77 years old, respectively), and mean age among patients without recurrence was higher than among patients with recurrence (77 vs. 73) (see also Table 2). The number of left- and right-sided CSDHs was similar (43% vs. 39%, respectively), and 18% were bilateral. 35% of the patients were taking antiplatelet drugs (aspirin, clopidogrel, ticlopidine or triflusal) and 12% were under anticoagulants (warfarin, acenocoumarol or enoxaparin). 19% of the patients had thrombocytopenia at the time of admission. Considering the patients who underwent BHC, nearly 65% were operated without using a post-operative drainage system, whereas in 23% a subdural and in 12% a subgaleal drain was left in place. We obtained a mortality and morbidity rate of 7% and 11%, respectively. Most of the deaths occurred due to aggravation of underlying clinical diseases or due to hospital-acquired infections (mainly pneumonia). Main causes of morbidity were persistent neurologic deficits, wound infection, empiema or suture dehiscence, symptomatic cerebral hemorrhage (intraparenchymal or acute SDH) requiring further management and seizures. We only considered seizures as a morbidity cause when at least one episode occurred after hospital discharge after surgery.

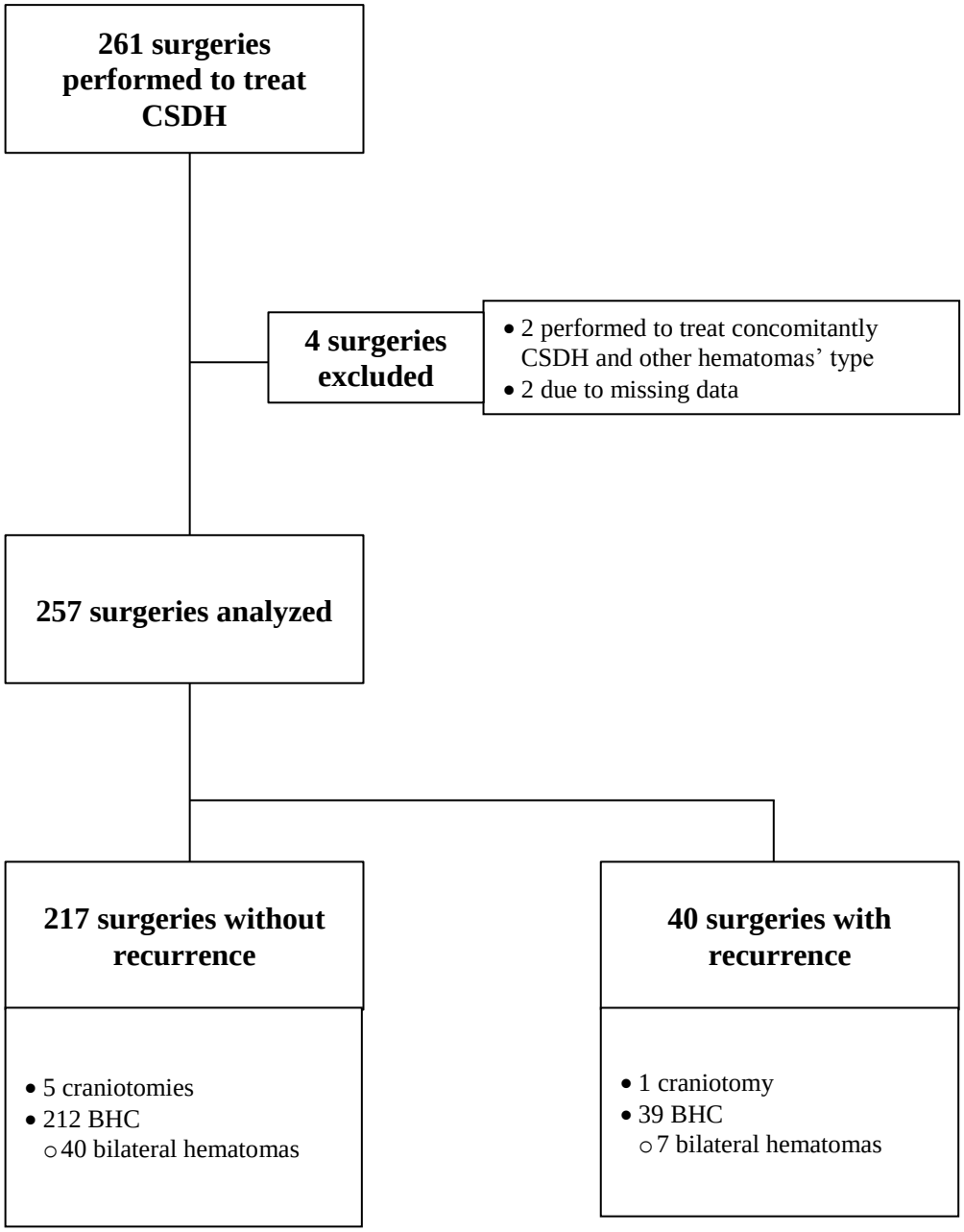

Figure 1 – Trial profile. BHC, burr-hole craniostomy; CSDH, chronic subdural hematoma

Table 1 – Patients characteristics and outcomes. Total *n* was 257, except for the following variables: antiaggregation and anticoagulation therapy (total *n* = 254), thrombocytopenia (total *n* = 227) and burr-hole craniostomy (total *n* = 249), due to missing data. SD, standard-deviation.

Total *n*		257
Gender	**Male *n* (%)**	163 (63.42%)
	Female *n* (%)	94 (36.58%)
Mean age years ± SD		76.04 ± 11.16
Hematoma location	**Left *n* (%)**	110 (42.8%)
	Right *n* (%)	100 (38.91%)
	Bilateral *n* (%)	47 (18.29%)
Antiaggregation therapy *n* (%)		89 (35.04%)
Anticoagulation therapy *n* (%)		30 (11.81%)
Thrombocytopenia *n* (%)		43 (18.94%)
Burr-hole craniostomy	**With subdural drain *n* (%)**	56 (22.49%)
	With subgaleal drain *n* (%)	30 (12.05%)
	Without drain *n* (%)	163 (65.46%)
Mortality *n* (%)		18 (7%)
Morbidity *n* (%)		29 (11.3%)

Table 2 shows the association between the studied variables and recurrence of CSDH. Mean age among patients who had recurrent CSDH and were, therefore, reoperated was significantly lower than among those who did not have recurrent CSDH ($p = 0.03$). Patients taking anticoagulants showed a trend towards a higher risk of recurrence ($p = 0.19$). On the other hand, the use of subdural drainage showed a trend as protector factor against recurrence, as patients who did not receive a post-operative drainage system or receive a subgaleal drain had a higher recurrence rate when compared to those who received a subdural drain ($p = 0.14$). Patients who had recurrent CSDH had also higher morbidity rate ($p = 0.03$), but not higher mortality rate. Gender, bilateral hematomas, medication with antiplatelet agents, thrombocytopenia and subgaleal drain use did not seem to influence recurrence of CSDH in our series.

Table 2 – Factors related to recurrence of chronic subdural hematoma. SD, standard-deviation.

Variables		**With recurrence *n* (%)**	**Without recurrence *n* (%)**	***p* value**
Gender	**Male *n* (%)**	29 (72.5)	134 (61.75)	0.22
	Female *n* (%)	11 (27.5)	83 (38.25)	0.22
Mean age years ± SD		72.50 ± 12.26	76.69 ± 10.86	**0.03**
Hematoma location	**Left *n* (%)**	16 (40)	94 (43.32)	0.73
	Right *n* (%)	17 (42.5)	83 (38.25	0.6
	Bilateral *n* (%)	7 (17.5)	40 (18.43)	1
Antiaggregation therapy *n* (%)		16 (41.03)	73 (33.95)	0.47
Anticoagulation therapy *n* (%)		7 (17.95)	23 (10.7)	0.19
Thrombocytopenia *n* (%)		6 (16.67)	37 (19.37)	0.82
Burr-hole craniostomy	**Without subdural drain *n* (%)**	34 (87.18)	159 (75.71)	0.14
	Without subgaleal drain *n* (%)	33 (84.62)	186 (88.57)	0.43
	Without drain *n* (%)	28 (71.7949)	135 (64.2857)	0.46
Mortality *n* (%)		2 (5)	16 (7.37)	0.75
Morbidity *n* (%)		9 (22.5)	20 (9.22)	**0.03**

IV. Discussion

1. Interpretation of the results

We obtained a recurrence rate of 15.6%, which is similar to other reports [1, 30-33]. Our series was also comparable to previous studies in terms of gender and age prevalence, with a mean age of 76 years old and a male predominance [31, 33]. Gender was not associated with higher recurrence rates, which is in agreement with other works [28, 32]. Surprisingly, mean age among patients who had recurrence of CSDH was lower than among those who did not have recurrence, and this difference was statistically significant. Borger et al. showed that patients above the age of 85 presented lower recurrence rates, yet carried a greater risk for other complications [34]. Another study also found a lower mean age among patients in the recurrent group when comparing to those in the non-recurrent group, but, unlike our result, the difference was not significant [35]. We did not find any article reporting younger age as a risk factor for recurrent CSDH. Our unexpected result could be explained by the fact that we only considered as recurrent CSDH when the hematoma was reoperated on (see Materials and methods), and reoperation might have been more frequent among younger patients. Although current data suggests that surgical treatment is safe in elderly patients [34], there are always operation-associated risks, and we might have tried to follow a more conservative strategy among those who were older. The definitions of recurrence are highly variable between studies, even in the subgroup of those looking specifically for this outcome [36], and this heterogeneity may explain the discrepancy of results in the literature.

Nearly 18% of the CSDHs were bilateral, which is consistent with earlier reports [10, 31], as well as a slightly more frequent location of CSDH on the left side (43%) [31]. Although some authors consider bilaterality a risk factor for recurrence of CSDH [37], others did not find the same association [33]. Like the latter, we did not observe an increased recurrence rate in bilateral CSDHs. One study concluded that bilateral CSDHs were independent predictors for reoperation due to surgical complications [30], but not necessarily due to recurrence of the hematoma.

In our study, a considerable number of patients were taking antiplatelet or anticoagulant medication at admission (35% and 12%, respectively), suggesting that these drugs are important risk factors for CSDH. Attention should be paid on the

possible adverse effects of these medications, considering the fact that there is an increasing number of users, especially among the elderly [28]. In our series, antiplatelet agents were not associated with an increased risk of recurrence. Similar results are found in other reports [28, 31, 33, 37]. Wada et al. reported a significant influence of antiplatelet therapy on the recurrence of CSDH, but not if the surgery was delayed for more than 3 days after discontinuation of the drug [29], which can explain our observation.

We found that usual treatment with anticoagulant drugs before surgery had a trend towards a higher recurrence rate. Schwarz et al. also reported that patients receiving vitamin K antagonists had a tendency towards a higher risk of surgically-relevant hematoma re-accumulation [30]. Other studies showed a significant association between the use of anticoagulants and higher recurrence rates [28, 33]. Mori and Maeda demonstrated that the administration of anticoagulant agents was significantly correlated with poorer brain re-expansion after hematoma evacuation [10], which could lead to higher risk of re-accumulation. However, results are conflicting, and some of the studies that reported no association with antiplatelet agents and recurrence, also did not find an association between anticoagulants and recurrence [31, 37].

In our study, there was no association between the presence of thrombocytopenia at admission and recurrence rate after surgery. This lack of association can be easily explained when we consider the fact that, when thrombocytopenia was initially detected, surgery was done under platelet transfusion. In our bibliographic search, we found no other studies that analyzed this variable as a possible risk factor for recurrence.

According to many authors, the placement of subdural closed-system drainage after BHC is associated with better outcomes (less recurrence and mortality rates) [1, 5, 7, 20, 38]. Using a post-operative drain is currently becoming widespread, and it is deemed to be the standard procedure [1, 38]. According to our results, when comparing the group of patients who did not receive any post-operative drain with those who did receive a subdural or a subgaleal drain, the first group did not present a statistically significant or even a trend towards higher recurrence rate. This finding would be in agreement with that of Stanisic et al., who did not demonstrate any relationship between recurrence and use of drainage [32]. However, we found a trend towards the use of a subdural drain as a protective factor for CSDH recurrence. Most studies seem to find no overall statistically significant differences between subgaleal and subdural drainage [1,

5], but, according to Bellut et al., there may be a tendency towards a lower recurrence with placement of subdural drain [25], which is consistent with our result.

Our mortality and morbidity rates were comparable to those found in the literature (7% and 11%, respectively) [1, 7]. Patients who had recurrent CSDH presented statistically significant higher morbidity rate, which emphasizes the need of reducing recurrence rates in order to achieve better outcomes to our patients. Recurrence was not, however, associated with higher mortality rates.

2. Limitations

Our study has some limitations that must be taken into account when interpreting the results. First, this was a retrospective study, subject to sources of bias and variation, mainly due to heterogeneity in records, resulting in a high number of missing data. Second, due to the sample size, there probably is a lack of adequate statistical power to detect a significant difference in variables studied. Third, there were multiple physicians involved in the surgical management of the patients with CSDH, and some operator-associated variability may have been present. The decision for reoperation of the CSDH after initial surgery was also physician-dependent, and a different number of recurrent cases might have been obtained if a standardized guide would have been followed.

3. Conclusions

On the basis of our results, recurrence of CSDH after initial surgical evacuation was associated with increased morbidity rate. Patients who presented with recurrent CSDH and underwent further reoperation were significantly younger than patients who did not have recurrence. There was a trend towards a higher risk of recurrence in patients who were usually treated with anticoagulant drugs prior to the surgery, and in patients who did not receive a subdural post-operative drain. There was, however, no significant association between gender, bilateral CSDHs, usual medication with antiplatelet drugs prior to the surgery, thrombocytopenia prior to the surgery, use of subgaleal post-operative drain or absence of post-operative drain and recurrence.

V. Acknowledgments

First, I would like to thank my thesis advisor, Dr. Alexandra Santos, for all her help, knowledge and guidance throughout this work. I would like to express my gratitude to Dr. José Cabral, director of the Neurosurgery department of CHLO, for approving the performance of this study in this institution. Last but not least, I would like to thank my Mother for supporting and believing in me. This accomplishment would not have been possible without them.

VI. References

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